Clinical Experience and Results of a Sentinel Health Investigation Related to Indoor Fungal Exposure

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This is a review of exposure conditions, clinical presentation, and morbidity of children and adults with indoor fungal exposure such as toxic *Stachybotrys chartarum*. Indoor exposure was characterized using different methods including microscopic, culture, cytotoxicity screening tests, and chemical analyses. Clinical case histories and physical and laboratory findings are presented of children (age < 18 years, n = 22; mean age 9 years; 60% females) and adults (age > 18 years, n = 125; mean age 39 years, 67% females) who consulted an environmental health specialty clinic. In the pediatric patients' exposure history, widespread fungal contamination of water-damaged building materials with known toxic or allergic fungi was identified. Primarily disorders of the respiratory system, skin, mucous membranes, and central nervous system were reported. Some enumeration and functional laboratory abnormalities, mainly of the lymphatic blood cells, were observed, although no statistically significant differences were found. IgE or IgG fungi-specific antibodies, used as exposure markers, were positive in less than 25% of all tested cases. In an evaluation of a symptomatic girl 11 years of age (sentinel case investigation) living in an apartment with verified toxigenic fungi (i.e., *S. chartarum*), several health indicators showed improvement after exposure cessation. *Key words*: allergy, bioaerosol, exposure, fungi, health, morbidity, mycotoxins, *Stachybotrys*, toxicity. — *Environ Health Perspect* 107(suppl 3):489–494 (1999).
http://ehpnet1.niehs.nih.gov/docs/1999/suppl-3/489-494johanning/abstract.html

Indoor exposure to fungi such as toxin-producing *Stachybotrys chartarum* (aka *Stachybotrys atra*) growing on wet building materials is gaining recognition as an important but challenging environmental risk factor for a variety of illnesses with public health implications (*1,2*). *S. chartarum* has been associated with serious adverse health effects in animals and humans and has in the past been found primarily in agricultural environments (*3*). High exposure levels of airborne pathogenic fungi in the work environment have been reported among farmers, woodworkers, and composting waste workers but may also be found among hospital and office workers or occupants of homes with significant water damage or with defective ventilation systems (*4–7*). In recent medical/epidemiologic investigations, an association has been described between high exposure to *S. chartarum* and toxic inflammatory effects in infants (*8–10*), in office workers handling moldy paper materials and breathing fungal-contaminated air (*11,12*), and in courthouse workers (*13*). These effects are thought to be related to toxic metabolites (mycotoxins) produced by certain fungi such as those in the genera *Stachybotrys*, *Aspergillus versicolor*, *Penicillium*, *Trichoderma*, and *Fusarium*.

S. chartarum appears clinically important because it produces biologically very potent mycotoxins such as trichothecenes (i.e., satratoxins) and spirolactons that interfere with protein synthesis on the DNA level and the cellular or humoral immune system in *in vitro* systems (*14,15*). The production of mycotoxins depends on environmental conditions and substrates and is not evident by macroscopic growth characteristics (*16,17*).

This study describes the health problems of a group of selected children who consulted an environmental health specialty clinic and compares those findings to those for adults with similar fungal exposure history. Further, the results of a sentinel case investigation are presented as an example of a positive health intervention outcome (secondary prevention).

Methods

Study Group Selection and Description

This is a descriptive study of patients evaluated in an ambulatory occupational and environmental health clinic, including self- and physician-referred patients primarily from the northeastern United States. A sample of patients less than 18 years of age was selected as a pediatric

sample because at that age completion of major organs and lymphoid maturity are achieved. The pediatric sample (age < 18 years, n = 22; mean age 9 years; 60% females) and a sample of adult patients (age > 18 years, n = 125; mean age 39 years, 67% females) were included if they had a verifiable history of indoor exposure to fungal air contaminants and if they had completed a standardized health symptom questionnaire. Fungal exposure was considered positive if industrial hygiene survey information and data confirmed the presence of fungi and significant moisture problems (leaks, flooding, condensation, etc.). In addition, for comparison, descriptive data from an earlier study are presented that included well-documented exposure and that used the same core questionnaire. The earlier study included a nonexposed adult population with similar demographics as a control group (*11*).

Health Symptoms Survey

The health symptoms survey had been adapted with slight modification from the Mount Sinai Medical Center Fungal Health Survey Questionnaire (*11*). Cumulative symptom complex scores were computed by combining separate questions related to particular organs: upper respiratory system (nasal irritation, burning, itchiness, stuffiness and congestion, nasal bloody discharge, throat irritations, and soreness); lower respiratory system (cough, shortness of breath, wheezing, chest congestion, and tightness); central nervous system (severe headaches, concentration problems, irritability, dizziness or lightheadedness, sleeping

problems, fatigue); eyes (burning, irritation, blurry vision); skin (burning, erythematous rash, hair loss); constitutional (low-grade fever, tender/swollen lymph nodes, flulike symptoms), and history of previously diagnosed allergy.

Laboratory Testing

Laboratory tests were performed to study red and white blood cells, multichemistry, and immunological parameters. The medical laboratory tests were analyzed by licensed commercial labs following standard quality assurance procedures (IBT Laboratory, Kansas, MO; Specialty Laboratory, Inc., Santa Monica, CA). To evaluate possible type I allergic reactivity, allergen-specific IgE was tested in a panel for *Cheatomium globosum; Aspergillus fumigatus; Cladosporium; Penicillium notatum; S. atra;* mouse, rat, and pigeon serum proteins; and American cockroach. A panel of IgG was measured and considered as marker of exposure for *Micropolyspora faeni, Thermoactinomyces* spp., *Alternaria alternata, A. fumigatus, Aureobasidium pullulans, P. notatum, Phoma herbarum, Trichoderma viride,* pigeon droppings, pigeon serum, bovine serum, *Cladosporium,* and *S. atra.* Allergen testing material was provided by Pharmacia & Upjohn Diagnostics (Bridgewater, NJ).

Exposure Assessment

Indoor exposure to fungal materials was assessed and verified by experts in the field generally relying on test methods described by the American Industrial Hygiene Association field guide for the determination of biologic contaminants (*18*). Indoor exposure was characterized using microscopic, culture, and mycotoxin cytotoxicity screening tests (MTT). Subjects with a history of indoor fungal exposure that was deemed to be excessive or atypical compared to outside or other references were included in the analysis presented here.

Sentinel Case Example

In addition to the epidemiologic data, a clinical case example is presented here to illustrate the complexity of comprehensive exposure and health assessment and also to document the benefits of a positive environmental intervention outcome (exposure cessation). In the case investigation, the indoor environment and health complaints of a low-income family living in an apartment building in Spanish Harlem, New York, were examined. The apartment had a longstanding history of moisture problems

and widespread visible fungal growth on interior surfaces (> 100 ft^2). The mother of an eleven-year-old daughter had noticed that the general health of her daughter improved when she was away from the New York apartment. The daughter had a history of recurrent bouts of asthma, pneumonia, bronchitis, sinusitis, and middle ear disease. Upon return to the apartment, previous symptoms and illnesses recurred or worsened. Observations by the primary care providers confirmed this history. It should be noted that the daughter (index case/subject A) had a diagnosis of velo–cardio–facial syndrome (a variant of DiGeorge syndrome), which is associated with T-cell deficits due to thymic hypoplasia and an increased susceptibility to infections. Although this condition is associated with disorders similar to or identical with the studied fungal outcomes, this case was chosen nonetheless because the history of symptoms given by the mother suggested that environmental factors strongly influenced the girl's health. Other family members were also included in the case study, as they also reported variation of their health status dependent upon environmental changes. A suitable case control was not available and such a study was not feasible at the time of this investigation. However, the adult occupant of the apartment that was used as a control in the environmental assessment was asymptomatic and free of any atopic diseases.

We investigated the environmental conditions inside the apartment and compared them to outside conditions and a reference apartment inside the same building that did not have visible evidence of moisture and fungal problems (healthy adult occupant). In addition to the index case, the brother (subject B; 21 years of age) and the mother (subject C; 50 years of age) were studied because they reported symptoms, although less severe. Subject A (who had lived since birth in the apartment) and subject C spent most of a typical day inside, whereas subject B was only in the apartment during the night. The family was removed from the contaminated apartment and retested after a period of 8 weeks (pulmonary function and T-lymphocyte flow cytometry) and again after 4 months (lymphocyte flow cytometry). There were never any pets in the apartment. The apartment building had a known history of cockroach and rat infestation.

Fungal Exposure Sampling

Viable fungal air samples were collected on cornmeal agar and malt extract agar using a

single-stage (N6) impacter (Andersen Instruments Inc., Atlanta, GA) operated at a flow rate of 28.3 L/min for 2 min. Total airborne fungal materials (including nonviable spores) were sampled using an Arca sampling pump and Air-O-Cell air sampling cassettes (SKC, Inc., Eighty Four, PA) with a 15 L/min flow rate for 3 min. The cassettes were analyzed; results were reported in fungal structures per cubic meter of air.

Toxicity Screening

The MTT cytotoxicity screening test is particularly sensitive to *S. chartarum* toxins (i.e., Satratoxin). The MTT cell culture assay and a swine kidney target cell line were used as a direct method. Bulk samples were tested directly in the toxicity tests for presence of mycotoxins (*19,20*). The principle of this bioassay is based on the transformation of the yellow tetrazolium salt MTT by viable, living cells (via mitochondrial dehydrogenase) to purple - formazans. The optical density of the formazans can be measured by an enzyme-linked immunosorbent assay (ELISA) reader at a wavelength of 540 nm. Swine kidney monolayer cells (SK), known to be sensitive to mycotoxins, were used as target cells. The minimum concentrations of the test reagents to cause toxic effects were determined on the basis of the statistically determined values of 80% cleavage activity.

Cockroach Antigen Sampling

Dust samples were collected using filter media attached to a vacuum cleaner hose. Approximately 1 m^2 of floor surface was vacuumed. The dust samples were analyzed using an immunologic assay to identify the presence of a cockroach allergen (Bla g 1). Results are reported in micrograms of cockroach allergen per gram of dust ($\mu g/g$).

Pesticide Sampling

A 100-cm^2 area of floor surface was wiped with sterile gauze saturated with toluene. The sample wipes and bottles were prepared, and later all samples were scanned by the Wisconsin Occupational Health Laboratory (Madison, WI) for presence of pesticide contamination.

Dust mite or other animal antigens were not measured. (This was a winter period and no household animals were present.) Other chemical or organic compounds were not measured because the industrial hygienist did not observe any unusual presence or use of household chemicals. An indoor asbestos and lead screening was negative.

Results

Review of Clinic Records

The analysis of clinically recorded health symptoms and organ complaints of patients with a history of indoor fungal exposures showed a high prevalence (> 50% of all respondents) of symptoms of upper and lower airways, eyes, and central nervous system. Children also showed a high prevalence of symptoms, although the absolute percentage rate was slightly lower than that of adults (Table 1, Figure 1). Compared to the office workers with health problems associated with fungal exposure and the nonexposed controls, children appeared to complain slightly more about upper airway problems (symptoms related to rhinitis, sinusitis, laryngitis) and slightly less about lower airway problems (symptoms related to bronchitis, asthma, or pneumonitis). Skin, eye, and central nervous system complaints were present in more than 40% of respondents,

with similar high proportions for the adults. Excessive physical and mental fatigue (fatigue) was reported by about one-third of the children interviewed and by about half the adults (54%). The rate of preexisting and diagnosed allergy in patients was less than 20% and lower than in the comparison groups. The higher prevalence of symptoms among patients and exposed office workers relative to non-exposed controls was not likely due to group differences in age, gender, or smoking, as groups were similar on these potential confounders (except, of course, for the younger ages of children).

Five percent of the children had any evidence of specific IgE antibodies to tested fungal allergens (except *S. atra*), 9% had an IgE reaction (borderline values), and none had an elevated IgG (> 40 mcg/mL) to *S. atra*. None of these children had a specific antibody reaction to cockroaches. Complete lymphocyte and other immunoglobulin analysis were

available for only five children and are not reported here. On the basis of the review of available industrial hygiene data, about 90% of the children had verifiable exposure to higher-than-normal indoor levels of primarily *Penicillium* and *Aspergillus* spp., and at least 41% of the children had documented exposure to *S. atra*.

Sentinel Case Example

Results of the clinical evaluation showed that all three subjects had objective evidence of respiratory disorders (mixed restrictive and obstructive abnormalities) and abnormalities of the T-cell flow cytometry subgroups (Tables 2, 3). Subjects A and B had very low CD4 counts, although no histories of HIV infection or similar risk factor for low CD4 T-cell counts were evident except for the verified genetic defect (velo–cardio–facial syndrome) in the index case. The ratios of CD4/CD8 were low and remained low after removal (1.2–1.4) in all subjects. Subject A had a low positive elevation of IgE to *S. atra* (873 counts) with a borderline total IgE elevation of 138 (> 158 indicative of atopic allergy). Subject B had no IgE or IgG elevation. None of the subjects was allergic to cockroach allergen.

After leaving the apartment, all subjects reported a marked improvement and a partial resolution of their health problems. Less frequent and severe cough episodes, less chest discomfort, and fewer breathing problems, headaches, fatigue, and flulike symptoms were noted. Pulmonary function improved in all three subjects (Table 2) and the lymphocyte enumeration measured 8 and 16 weeks after removal (Table 3) appeared to show some minimal improvement in some parameters. The index case had a PWM and CON mitogen response abnormality during the exposure period (data not shown). The results of the T-lymphocyte function (mitogen proliferation) tests performed 16 weeks after removal were normal in all subjects. These results and the lack of clinically significant viral or bacterial infections after removal from exposure indicate only a minor remaining immunodeficiency, which could be explained by the known preexisting genetic abnormality.

Inside the apartment, approximately 70–100 m² of surface area (walls, ceilings, around the window air conditioning unit, the doors, and window frames) were covered with a blackish-colored growth. Airborne fungal counts (viable and nonviable) were significantly higher (10–200×) than the outside or the control apartment used as a reference (Table 4). Predominant

Table 1. Results and comparison of symptom survey after indoor fungal exposure.[a]

Organ system affected	Children (< 18 years of age) n = 22 (%)	Adults (≥ 18 years of age) n = 125 (%)	Office workers with fungal exposure (adults)[a] n = 53 (%)	Controls (adults)[a] n = 21 (%)
Respiratory system				
Upper airways	64	80	57	43
Lower airways	50	88	76	43
Skin	41	61	47	19
Eyes	50	66	57	19
Central nervous system	64	80	70	52
Constitutional	18	6	28	5
Fatigue	32	54	24	5
Previous diagnosis of allergy	18	25	60	48
Age (years)	9.3	44.5	34.8	37.5
Female gender (%)	60	67	73.6	52.4
Smoker (%)	0	22.4	18.9	19

[a]Proportion of subjects reporting at least one symptom in each symptom complex. [b]Data from Johanning et al. (11).
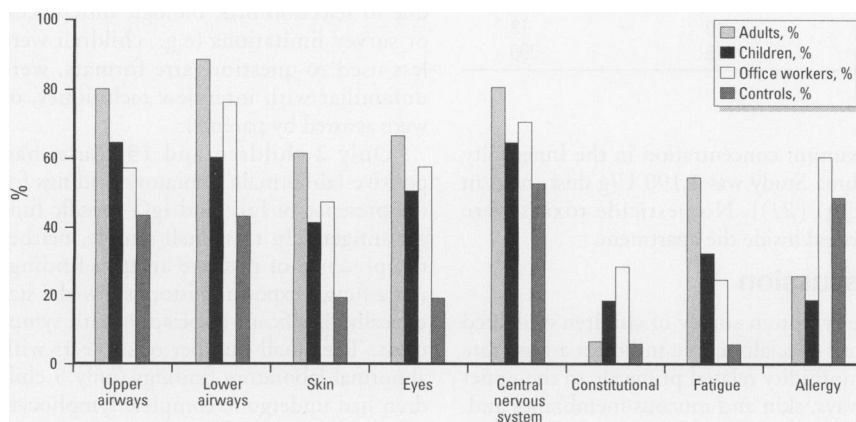

Figure 1. Health survey: children vs. adults. For explanation of office workers and controls, see text.

Table 2. Pulmonary function test before and after exposure cessation (intervention in case example).[a]

	Preintervention	Postintervention
Subject A (index case)		
FVC (L/% of predicted)	1.65 (65)	2.17 (76)
FEV1 (L/% of predicted)	1.60 (65)	1.73 (69)
Ratio (%)	96	80
Subject B		
FVC (L/% of predicted)	4.7 (87)	4.9 (90)
FEV$_1$ (L/% of predicted)	3.3 (71)	3.8 (81)
Ratio (%)	70	78
Subject C		
FVC (L/% of predicted)	1.98 (67)	2.17 (77)
FEV$_1$ (L/% of predicted)	1.7 (70)	1.9 (81)
Ratio (%)	87	87

[a]All subjects are nonsmokers; predicted normals based on height, gender, race, weight, age. For children <18 years of age, data from Polgar and Promadhat (24); data for adults >18 years of age, data from Knudson et al. (25,26).

Table 3. Lymphocyte screening results (case example).

Test	Preintervention	Postintervention (8 weeks)	Postintervention (16 weeks)
Subject A (index case, 12 years of age)			
Mature T cells CD3 (%)	67	65	62
Absolute CD3 (#)	601	358	450
Helper CD4 (%)	26	30	31
Absolute CD4 (#)	233	165	230
Suppressor CD8 (%)	22	19	24
Absolute CD8 (#)	197	105	180
CD4/CD8	1.2	1.6	1.3
NK cells (%)	9	16	21
NK cells (#)	81	88	150
Subject B (22 years of age)			
Mature T cells CD3 (%)	62	65	58
Absolute CD3 (#)	558	619	672
Helper CD4 (%)	34	34	28
Absolute CD4 (#)	306	324	330
Suppressor CD8 (%)	25	28	25
Absolute CD8 (#)	225	267	294
CD4/CD8	1.4	1.2	1.1
NK cells (%)	24	21	24
NK cells (#)	216	200	276
Subject C (51 years of age)			
Mature T cells CD3 (%)	72	71	71
Absolute CD3 (#)	1493	886	1110
Helper CD4 (%)	38	39	43
Absolute CD4 (#)	788	487	670
Suppressor CD8 (%)	35	31	41
Absolute CD8 (#)	726	387	640
CD4/CD8	1.2	1.3	1.1
NK cells (%)	15	10	13
NK cells (#)	311	125	200

NK, natural killer.

indoor airborne fungi were *Cladosporium, Aspergillus, Penicillium,* and *S. chartarum.* Bulk samples taken from the problem apartment showed a high concentration of *S. chartarum, A. versicolor,* and *Cladosporium.* All bulk samples taken from the home (bedroom, bath, and kitchen) were toxic to highly toxic in the MTT screening test.

Cockroach allergen Bla g 1 in sampled floor dust was considered high, based on the classification by the National Cooperative Inner-City Asthma Study, although the maximum concentration in the Inner-City Asthma Study was 1,190 U/g dust [median 8 U/g) (21)]. No pesticide toxins were detected inside the apartment.

Discussion

The symptom survey of children evaluated in our specialty clinic indicates a high rate of morbidity related primarily to the upper airways, skin and mucous membranes and, to a lesser degree, lower airways. In all cases we confirmed that these children had all been living in indoor environments with high levels of fungi, often species not normally found indoors or in such concentrations compared to the outside air (i.e., *S. chartarum, A. versicolor, Trichoderma).* Our results are in agreement with a number of previous studies. A recent review of the literature investigating the association of wheeze and cough and damp or mold found that the adjusted odds ratio for an increased risk of children was generally in the range of 1.5–3.5 (22). The high rate (about two-thirds) of central nervous system problems among children from moldy homes suggests a complex exposure-associated morbidity reaction with a pathologic pathway that cannot readily be explained by atopy or allergy (IgE-mediated). The health complaints summarized by organ system were similar for children compared to adults, although the absolute percentage rate of complaints was slightly lower for children. The rate of reported symptoms was higher than that of a nonexposed adult control group in almost all categories except for a previous diagnosed history of allergy. None of the queried children had evidence of an allergy to cockroaches, which has been described as an important predictor of environmental-associated asthma (21). On the basis of our assessment of the clinical cases, morbidity related in time and place to indoor fungal exposure appears to be widespread in environments with a history of flooding, water leaks, moisture problems, and ventilation defects that resulted in intense fungal growth on interior building materials or furniture.

Differences were not analyzed for statistical significance because of methodological issues and limitations such as small sample size and different time and location of measurements. The response variations and group differences may be due to selection bias, biologic differences, or survey limitations (e.g., children were less used to questionnaire formats, were unfamiliar with interview techniques, or were assisted by parents).

Only 2 children and 13 adults had positive (abnormal) laboratory findings for the presence of IgE- and IgG-specific fungal antigens. In this small sample, neither the presence of positive antigen findings nor a fungal exposure history showed a statistically significant association with symptoms. The small number of subjects with abnormal laboratory findings (only 5 children had undergone complete lymphocyte testing) did limit the statistical power of analysis of group differences in laboratory

Table 4. Sentinel case exposure assessment—bulk and air sampling results.[a]

	Quantity	Comments (predominant)
Fungiculture (CFU/m³) (viable)		
Inside	1993 to >7067	Clado., Asp., PNC, Stachy.
Control	194 to 336	Clado, PNC
Fungal structure/m³ (nonviable)		
Inside	180,000 to 658,000	ASP/PNC like, Clado., Stachy.
Control	3656 to 4700	Clado, *Basidiospores*
Bulk sample (CFU/g)		
Wallpaper (living room)	1.6–2 × 1,000,000	Stachy. (50–66%), *A. versicolor,* PNC
Toxicity tests (MTT screening)		Electron microscopy[b]
Wallpaper (bedrooms, samples 1–3)	Toxic to highly toxic	Stachy. +++, PNC+, ASP+
Kitchen (wallpaper)	Highly toxic	Stachy. ++ *Fusarium*+ *Trichoderma*+
Nonfungal tests		
Cockroach allergen (Bla g1)	18 to 36	Microgram per gram dust
Pesticides	0	None detected

Abbreviations: Clado, *Cladosporium;* Asp, *Aspergillus;* PNC, *Penicillium;* Stachy, *Stachybotrys;* CFU, colony-forming units; MTT, mycotoxin cytotoxicity screening tests. [a]Various test protocols described in "Methods." [b]+ to +++ = low to high quantity.

findings. The differences in laboratory test results may be related to a variety of factors including the differences in exposure duration, latency, timing of laboratory testing relative to exposure and testing, and temporary medical treatment effects. A study of a larger number of children with similar exposure (children in kindergarten or schools) that included testing of biologic markers at the same time would be beneficial for epidemiologic studies. Presently there is not a reliable mycotoxin biomarker available for clinical screening studies. Therefore, clinicians rely on indirect laboratory effects measures such as T-lymphocyte responses and immunoglobulins counts. Advances in immunology, laboratory, and diagnostic methods may ease clinical diagnosis in the future.

In the case example investigation, a key factor was the reported history of variability of health complications depending on the indoor environment, i.e., the dramatic health improvement away from the fungal exposure inside the apartment. We presented this case example because it appears to demonstrate that such fungal exposure can significantly aggravate and complicate pre-existing immunological disease. The exposure was not only affecting the index case but also the brother and mother who shared the apartment with her but had no history of genetic abnormalities. Inside the apartment we identified very high levels of fungi indoors, with a predominance of *Cladosporium* and toxigenic *S. chartarum.* The presence of airborne *S. chartarum* in indoor environments is considered by experts to be highly uncommon in normal buildings and unacceptable from a public health perspective. The MTT cytotoxicity tests showed that

all samples taken from the girl's home environment had toxic metabolites (such as trichothecene) in the fungal materials. The fungal mass (spores) would have become airborne when disturbed.

Blood lymphocyte changes effecting the T-lymphocyte differentiation and subpopulation proportion were measured as in previous studies (*11,23*). Changes of the T-lymphocyte population were demonstrated in *in vitro* and *in vivo* studies but remain difficult to interpret on an epidemiological level because of only very small differences and variations in observed trends. In our case example, some lymphocyte parameters showed improvement after exposure cessation, but these may be within laboratory and normal daily variations. Only the index case had genetic evidence of a deletion of 22q11.2, confirming a velo-cardio-facial syndrome (DiGeorge variant). Cockroach antigen (Bla g1) exposure, although present in high concentration, did not result in measurable allergies in any of the apartment occupants. On the basis of available data and the observed health improvement with exposure cessation, we concluded that indoor fungal exposure was the probable contributing cause of the health problems associated with living in this apartment. Some other unidentified agents or conditions may have also contributed to the improved outcome, although we think this is very unlikely under the circumstances. Studies of health outcomes related to bioaerosol exposure appear more complicated than monoagent chemical exposure studies because several biologic components (i.e., β-glucans, microbial volatile organic compounds, endotoxins, allergen, mycotoxins) may have independent or combined effects.

It is our clinical experience that symptoms associated with mold exposure tend to resolve with exposure avoidance and symptomatic treatment. In some individuals, symptoms may last several weeks to months after exposure control and in some rare cases may not be reversible at all. A highly increased sensitivity with recurrent fungal exposure has been noted by some individuals. These variations in the postexposure periods may be related to differences in the exposure duration, intensity, and particular conditions (different fungal species), the biologic differences of the immune reaction of exposed individuals, and the type of medical intervention or treatment.

Children with preexisting, significant immunological weaknesses and defects are at increased risk and should be protected from unnecessary fungal exposure. Long-term benefits of such intervention (secondary prevention) and related health indicators should be studied more systematically. Fungal exposure in indoor environments should be included in future environmental respiratory and immunologic disease studies, in addition to already known indoor pollutants. It is necessary for the physician examining a child with complex respiratory problems, allergy, nervous system disorders, and perhaps other organ system problems, to inquire about problems in the home such as chronic water leaks, extensive interior condensation, flooding, and especially visible fungal growth on interior building materials. In many cases, effective fungal exposure control and avoidance may be all that is needed to achieve a significant improvement in the child's health.

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